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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,195	06/30/2005	Patricia Salvati	373987-004US (396982)	7746
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EXAMINER				
JAVANMARD, SAHAR				
ART UNIT		PAPER NUMBER		
1617				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/541,195

Applicant(s)

SALVATI ET AL.

Examiner

SAHAR JAVANMARD

Art Unit

1617

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 December 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5,9,10,12-14 and 16-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5,9,10,12-14 and 16-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
- Paper No(s)/Mail Date 12/09/08.
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 12/09/2008. Claim(s) 1-5, 9-10, 12-14 and 16-22 are pending. Claim(s) 1, 9, 10 and 16 have been amended. Claim(s) 1-5, 9-10, 12-14 and 16-22 are examined herein.

Response to Arguments

Amendments to the claims and specification are hereby acknowledged.

Applicant's arguments with respect to the 102(b) rejection of claims 1-4, 9-10, 12, 13 and 19-22 as being anticipated by Pevarello (WO 99/35125) has been fully considered but are not persuasive as Applicant is now arguing based on amended claims. Since Applicant has amended the claims, said rejection is hereby withdrawn.

Applicant's arguments with respect to the 103(a) rejection of claims 5, 14, 16-18 and 23 as being obvious over Pevarello (WO 99/35125) have been fully considered but are not persuasive as Applicant is now arguing based on amended claims. The 103(a) rejection is maintained for reasons of record but is modified as necessitated by Applicant's amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-4, 9-10, 12, 13 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pevarello et al. (WO 99/35125) in view of Strittmatter (*Headache*, 1997).

Pevarello teaches compounds of formula I and pharmaceutically acceptable salts thereof (page 2, line 2- page 5, line 26) as therapeutic agents used for treating pain associated with damage or permanent alteration of the peripheral or central nervous

systems such as peripheral neuropathies e.g. trigeminal and post-therapeutic neuralgia, diabetic neuropathy, glossopharyngeal neuralgia, radiculopathy, neuropathy secondary to metastatic infiltration, adiposis dolorosa and burn pain and central pain conditions such as those following stroke, thalamic lesions and multiple sclerosis (page 6, lines 13-22).

Pevarello further discloses a dosing regimen where the compounds of interest, specifically (S)-2-[4-(3-fluorobenzyloxy)benzylamino]-propanamide, were administered in doses of 7.5, 15.0, 30.0 and 60.0 mg/kg (page 12, lines 20-26).

Pevarello teaches that said compounds are useful in mammals, including humans, as analgesic agents (page 15, lines 5-6).

The compounds can be administered in a variety of dosage forms including orally, rectally and parenterally (page 16, lines 5-9).

Pevarello does not specifically teach disorders of trigeminovascular activation.

Strittmatter discloses a study that teaches that substance P plays an important role as a pain-inducing excitatory neurotransmitter in neurogenic inflammation and that clinical studies have confirmed this role of substance P as an activator of afferent nociceptive structures in the anatomic region of the trigeminal nerve. Strittmatter further teaches that together with the fact that recent studies stress the importance of the trigeminovascular system in trigeminal neuralgia, supports the hypothesis that continuing neurogenic inflammation is an important factor in the pathogenesis of trigeminal neuralgia (page 214, "Comments" section).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the compounds of formula I taught by Pevarello for the treatment of trigeminal neuralgia and also employed them for the treatment of disorders of trigeminovascular activation. One would be motivated to do so because as taught by Strittmatter, the trigeminovascular system plays an important role in trigeminal neuralgia. Thus by treating trigeminal neuralgia as taught Pevarello, one would in essence be treating a disorder that is trigeminovascularly activated.

Claim 5 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pevarello et al. (WO 99/35125) in view of Strittmatter (*Headache*, 1997) as applied to claims 1-4, 9-10, 12, 13 and 19-22 above.

Pevarello is discussed above.

Pevarello teaches (S)-2-[4-(3-fluorobenzoyloxy)benzylamino]-propanamide however does not specifically teach the (+) optical isomer as recited in claim 5.

As per claims 17 and 18, 2-[4-(2-fluorobenzoyloxy)benzylamino]-propanamide and 2-[4-(3-chlorobenzoyloxy)benzylamino]-propanamide are taught, respectively, however Pevarello does not specifically teach the S-(+) optical isomer.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have known that the (S) racemate of 2-[4-(3-fluorobenzoyloxy)benzylamino]-propanamide as taught by Pevarello is a mixture of (+)

and (-) isomers. Furthermore, one of ordinary skill in the art would also have known that 2-[4-(2-fluorobenzyloxy)benzylamino]-propanamide and 2-[4-(3-chlorobenzyloxy)benzylamino]-propanamide are a mixture of enantiomers in which each enantiomer further comprises of two optical isomers.

The fundamentals of optical activity and stereoisomerism are well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have known how to resolve the racemic mixture and would have been motivated to do so with the reasonable expectation of achieving enantiomers having substantially different pharmacological activity. It appears as though applicant has determined experimentally what a person of ordinary skill in the art would have expected, namely, that the racemic mixture of the prior art may be separate (+) and (-) enantiomers possessing substantial different pharmacological activity. This is an expected result. It is well established that expected beneficial results are evidence of obviousness of a claimed invention just as unexpected beneficial results are evidence of unobviousness. *In re Skoll*, 523 F. 2d 1392, 187 U.S.P.Q. 481 (C.C.P.A. 1975); *In re Skoner*, 517 F. 2d 947, 186 U.S.P.Q. 80 (C.C.P.A. 1975); *In re Gershon*, 372 F. 2d 535, 152 U.S.P.Q. 602 (C.C.P.A. 1967);

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pevarello et al. (WO 99/35125) in view of Strittmatter (*Headache*, 1997) as applied to claims 1-4, 9-10, 12, 13 and 19-22 above.

Pevarello is discussed above.

Pevarello does not teach a dose range from 0.5-5 mg/kg.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have administered the drugs taught by Pevarello in the dose range of 0.5-5 mg/kg. The dosage regimen of the compounds of interest is deemed to be a manipulatable parameter practiced by a person skilled in the art to obtain the best possible range depending on the route of administration and the weight of the subject.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pevarello et al. (WO 99/35125) in view of Strittmatter (*Headache*, 1997) in further view of Goadsby (*Annals in Neurology*, 1993) as applied to claims 1-4, 9-10, 12, 13 and 19-22 above.

Pevarello is discussed above.

Pevarello does not specifically teach a head pain condition wherein the condition is migraine.

Goadsby teaches that migraines are intimately linked to the trigeminal innervation of the cranial vessels, the trigeminovascular system (abstract; page 48, column 1, 1st paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have also administered the compounds employed by Pevarello to have

also treated migraine as the disorder. As discussed above, the trigeminovascular system plays an important role in trigeminal neuralgia based on the teachings of Strittmatter. As further taught by Goadsby, migraines are also intimately linked to the trigeminovascular system. Thus it would have been obvious to one of ordinary skill to have also treated migraines with the compounds of formula I taught by Pevarello because both trigeminal neuralgia and migraines are linked to the trigeminovascular system.

Conclusion

Claims 1-5, 9-10, 12-14 and 16-22 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617

